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=> s targretin or bexarotene
             1 TARGRETIN
             1 BEXAROTENE
L1           1 TARGRETIN OR BEXAROTENE

=> file biosis embase caplus medline cancerlit
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=> s leukemia
L2       732683 LEUKEMIA

=> s l1 and l2
L3           73 L1 AND L2

=> s l3 and py<=2000
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   4 FILES SEARCHED...
L4           19 L3 AND PY<=2000

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L5   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:772398  CAPLUS
DN   133:344604
TI   Compositions and methods using a retinoid X receptor agonist and a protein
     kinase A activator for treatment of hyperproliferative diseases
IN   Benoit, Gerard; Gronemeyer, Hinrich; Lanotte, Michel; Gottardis, Marco
PA   Bristol-Myers Squibb Company, USA; Institut National de la Sante et de la
     Recherche Medicale; Centre National de la Recherche Scientifique;
     Universite Louis Pasteur
SO   PCT Int. Appl., 80 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 2000064260         A1    20001102    WO 1999-US8908          19990423 <--
         W:  AU, CA, JP, MX
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
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PT, SE

	AU 9941815	A1	20001110	AU 1999-41815	19990423 <--
	AU 773928	B2	20040610		
	EP 1173061	A1	20020123	EP 1999-925558	19990423
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002542268	T2	20021210	JP 2000-613263	19990423
PRAI	WO 1999-US8908	A	19990423		

AB The invention provides compns. comprising a retinoid X receptor agonist and an agent capable of activating protein kinase A. The invention also provides methods of treating hyperproliferative diseases by administering a retinoid X receptor agonist and an agent capable of activating protein kinase A.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:658036 CAPLUS
DN 133:247304
TI Benzamide analogs as nuclear receptor agonists and reinforcement agents for treatment of cell proliferation-, hormone-, and vitamin-related diseases
IN Suzuki, Tsuneji; Ando, Tomoyuki; Tsuchiya, Katsutoshi; Nakanishi, Satoru; Saito, Akiko
PA Mitsui Chemical Industry Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2000256194	A2	20000919	JP 1999-236850	19990824 <--
PRAI	JP 1999-795	A	19990106		

OS MARPAT 133:247304
AB Benzamide analogs (I; Markush's structures given) and their pharmacol. acceptable salts are claimed as nuclear receptor agonists and reinforcement agents for treatment of cell proliferation-, hormone-, and vitamin-related diseases, including cancer. I induced **leukemia** cell differentiation and potentiated the antitumor effect of the PPAR receptor agonist pioglitazone and the retinoid LGD1069.

L5 ANSWER 3 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2000368049 EMBASE
TI Differentiate or Die: The view from Montreal.
AU Thiele C.J.; Gore S.; Collins S.; Waxman S.; Miller W.
CS C.J. Thiele, National Cancer Institute, Bethesda, MD, United States
SO Cell Death and Differentiation, (2000) 7/10 (1014-1017).
Refs: 1
ISSN: 1350-9047 CODEN: CDDIEK
CY United Kingdom
DT Journal; Conference Article
FS 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L5 ANSWER 4 OF 16 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2000:223068 BIOSIS
DN PREV200000223068
TI Oral bexarotene capsules as treatment for all stages of refractory or

persistent CTCL.
AU Duvic, M. [Reprint author]; Martin, A.; Hymes, K.; Washenik, K.; Heald, P.; Wood, G.; Myskowski, P.; Crowley, C.; Yocum, R.
CS MD Anderson, Washington University, Seattle, WA, USA
SO Journal of Investigative Dermatology, (April, 2000) Vol. 114, No. 4, pp. 776. print.
Meeting Info.: 61st Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA. May 10-14, 2000.
CODEN: JIDEAE. ISSN: 0022-202X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 31 May 2000
Last Updated on STN: 5 Jan 2002

L5 ANSWER 5 OF 16 EMBASE on STN
AN 2000376999 EMBASE
TI Retinoids in breast cancer prevention and treatment. A review of the literature.
AU Baj G.; Arnulfo A.; Deaglio S.; Mallone R.; Vigone A.; Rosa M.; Giana M.; Villa L.; Malavasi F.; Surico N.
CS Dr. N. Surico, Clinica Ostetrica e Ginecologia, Universita del Piemonte Orientale, Ospedale Maggiore di Novara, Corso Mazzini, 18, 28100 Novara, Italy
SO European Journal of Gynaecological Oncology, (2000) 21/4 (411-415).
Refs: 64
ISSN: 0392-2936 CODEN: EJGODE
CY Canada
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB During the last three decades, research focused on cancer treatment has led to the development of many cytotoxic agents. Despite the fact that these efforts have significantly improved the prognosis of certain malignancies such as some lymphomas, **leukemias** and testicular carcinomas, other tumors such as ovarian, lung and metastatic breast cancer are still associated with a poor prognosis. An innovative approach has recently emerged, thanks to a better understanding of tumor cell biology and many efforts are aimed at finding compounds capable of restoring a more differentiated phenotype to tumor cells, thereby reducing the tumor's aggressiveness and ultimately reverting it to its normal counterpart [1, 2]. Retinoids are the prototype of this new therapeutical approach called 'differentiation therapy'.

L5 ANSWER 6 OF 16 BIOSIS on STN
AN 2001:300231 BIOSIS
DN PREV200100300231
TI Induction of apoptosis in lymphoid **leukemia** cells: Differential effects of RAR and RXR retinoids with dexamethasone.
AU Gorgun, Gullu [Reprint author]; Foss, Francine M. [Reprint author]
CS Hematology/Oncology, Tufts New England Medical Center, Boston, MA, USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 132a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

Conference; (Meeting Poster)
LA English
ED Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002
AB Retinoids have been shown to regulate a number of cellular processes, including cell growth and differentiation. The identification of subfamilies of retinoid receptors (RARalpha,beta,gamma and RXR alpha,beta,gamma) has led to the development of ligands with specific binding affinities, Bexarotene (Targretin), is a selective RXR ligand which has been demonstrated to inhibit growth and induce apoptosis in HL60 cells and in epithelial cancer cell lines. Both oral and topical bexarotene have shown clinical efficacy in patients with cutaneous T-cell lymphoma, but the mechanism has not been elucidated. We examined the effects of bexarotene and the RAR-specific retinoid, ATRA, on cell growth and induction of apoptosis in the T-**leukemia** cell line, HUT78, NALM-6 pre-B cells, and fresh **leukemia** cells from patients with CLL. At concentrations of 10-5 to 10-10 M, we found growth inhibition but no apoptosis, as measured by change in Annexin V immunostaining or the expression of apoptosis-associated proteins, including PARP, Bad, Bcl-2 and BclXL. Because previous studies have demonstrated that the combination of steroids with ATRA induced apoptosis in myeloma cell lines, we investigated the effects of the addition of dexamethasone to cell lines exposed to either bexarotene or ATRA. A 3-fold enhancement in cytotoxicity was demonstrated by Annexin V immunostaining with the combination of 2X10-5M bexarotene+ 10-5M dexamethasone in the HUT78 T-cells compared to either drug alone, with no significant difference in cytotoxicity in the presence of 2X10-5M ATRA+ dexamethasone, whereas in the pre-B NALM-6 cells, there was a 5-fold enhancement in cytotoxicity with 2X10-5M ATRA+ dexamethasone but not bexarotene+ dexamethasone. In fresh CLL cells, 2X10-5M bexarotene alone induced apoptosis in 30-50% of the cells, whereas the combination of 10-5M dexamethasone and bexarotene induced apoptosis in 70-75% after 48 hours of exposure with the combination of bexarotene+ dexamethasone. These results suggest that RXR and RAR retinoid receptor ligands display differential effects in T and B-**leukemia** cells, perhaps dependent on their state of differentiation, and that the combination of retinoids and dexamethasone induce apoptosis to a more significant degree than retinoids alone. The combination of bexarotene and dexamethasone would be worthy of further investigation in the clinic.

L5 ANSWER 7 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999382621 EMBASE
TI The biologic basis for the use of retinoids in cancer prevention and treatment.
AU Kurie J.M.
CS Dr. J.M. Kurie, Dept. Thoracic-Head Neck Med. Oncol., University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States
SO Current Opinion in Oncology, (1999) 11/6 (497-502).
Refs: 61
ISSN: 1040-8746 CODEN: CUOOE8
CY United States
DT Journal; General Review
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Retinoids (vitamin A and related molecules) are biologic agents that have demonstrated, in preclinical and clinical models, potent activity in the prevention and treatment of a variety of malignancies. Presented in this article is a review of recent clinical studies and correlative laboratory findings that advance our understanding of the biologic basis for the use

of retinoids in cancer prevention and treatment.

L5 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:484939 CAPLUS
DN 129:104205
TI Treatment of disease states which result from neoplastic cell proliferation using PPAR-γ activators, and compositions useful therefor
IN Evans, Ronald M.; Tontonoz, Peter; Nagy, Laszlo
PA The Salk Institute for Biological Studies, USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9829113	A1	19980709	WO 1997-US24190	19971229 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2276288	AA	19980709	CA 1997-2276288	19971229 <--
	AU 9858112	A1	19980731	AU 1998-58112	19971229 <--
	EP 963199	A1	19991215	EP 1997-954303	19971229 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001507706	T2	20010612	JP 1998-530323	19971229
	AU 9942415	A1	19990930	AU 1999-42415	19990730 <--
	AU 742981 not instituted	B2	20020117		
	US 6646008	B1	20031111	US 2000-331535	20000222
	US 2004162354	A1	20040819	US 2003-627160	20030724
PRAI	US 1996-34813P	P	19961231		
	AU 1998-58112	A3	19971229		
	WO 1997-US24190	W	19971229		
	US 2000-331535	A3	20000222		

OS MARPAT 129:104205
AB In accordance with the present invention, it has been discovered that PPARγ is expressed consistently in tissues associated with each of a variety of disease states which result from neoplastic cell proliferation. It has further been discovered that maximal activation of PPARγ with exogenous ligand promotes terminal differentiation of primary cells which are otherwise subject to neoplastic cell proliferation. In accordance with another aspect of the invention, it has been discovered that RXR-specific ligands are also potent agents for induction of differentiation of cells expressing the PPARγ/RXRα heterodimer, and that simultaneous treatment of cells subject to neoplastic cell proliferation with a PPARγ-selective ligand, in combination with an RXR-specific ligand, results in an additive stimulation of differentiation. Thus, the effect of neoplastic cell proliferation can be ameliorated by treatment of cells undergoing neoplastic cell proliferation with PPARγ agonists, optionally in the further presence of RXR agonists, thereby blocking further proliferation thereof. Accordingly, compds. and compns. which are useful for the treatment of a variety of disease states which result from neoplastic cell proliferation have been identified and are described herein.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:385267 CAPLUS
DN 129:117505
TI Induction of differentiation in acute promyelocytic **leukemia** cells by 9-cis retinoic acid α-tocopherol ester (9-cis tretinoin tocoferil)
AU Makishima, Makoto; Umesono, Kazuhiko; Shudo, Koichi; Naoe, Tomoki; Kishi, Kenji; Honma, Yoshio
CS Department of Chemotherapy, Saitama Cancer Center, Research Institute, Saitama, 362, Japan
SO Blood (**1998**), 91(12), 4715-4726
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
AB Acute promyelocytic **leukemia** (APL) has a specific genetic rearrangement between the retinoic acid receptor (RAR)-α gene and the pml nuclear protein gene. All-trans-retinoic acid (ATRA) induces granulocytic differentiation of APL-derived cells and is used to treat APL patients. ATRA interacts with normal cells with RAR throughout the entire body, and when used at high doses or over a long duration, it induces several adverse side-effects. Development of drugs that selectively act on APL cells may increase the therapeutic efficacy of APL treatment as well as elucidate the mechanisms of responses to ATRA. In this study, 9-cis-retinoic acid α-tocopherol ester (9CTT) inhibited the proliferation of APL-derived NB4 and HT93 cells and induced differentiation markers, such as granulocytic maturation, nitroblue tetrazolium reduction and CD11b expression, in these cells. The effects of 9CTT on non-APL cells, including HL-60 and U937 cells, were much weaker than those on APL cells. Tretinoin tocoferil (TT), an α-tocopherol ester of ATRA, did not induce the differentiation of APL cells as effectively as 9CTT. The differentiation-inducing effects of 9CTT were inhibited by RAR antagonists. The 9CTT and TT similarly induced the transactivating activity of RARs, but were not effective on retinoid X receptors (RXRs). The 9CTT down-regulated the expression of PML/RAR-α protein more effectively than TT, which suggests that it may be involved in the selectivity of 9CTT against APL cells. The 9CTT enhanced the differentiation of APL cells induced by ATRA, 9-cis-retinoic acid, and synthetic retinobenzoic acids. Combined with 1α,25-dihydroxyvitamin D3 (VD3), 9CTT also more than additively induced the differentiation of APL cells. Thus, 9CTT alone or in combination with other retinoids or VD3, may be useful for the treatment of APL.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998277381 EMBASE
TI Retinoids as chemopreventive and therapeutic agents.
AU Sun S.-Y.; Lotan R.
CS R. Lotan, Department of Tumor Biology, University of Texas, M.D. Anderson Cancer Center, Houston, TX 77030, United States
SO Drugs of the Future, (1998) 23/6 (621-634).
Refs: 135
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Retinoids, naturally occurring and synthetic vitamin A metabolites and

analogs, exhibit promising antitumor effects in a variety of in vitro and in vivo model systems and in clinical trials. They inhibit carcinogenesis in various tissues in animal models, suppress premalignant human epithelial lesions and prevent second primary tumors following curative therapy for epithelial malignancies such as head and neck and lung cancer. Laboratory and clinical studies also indicate that retinoids have a potential as therapeutic agents. Retinoids inhibit cell proliferation and induce cell differentiation and apoptosis in various types of tumor cells. Significant therapeutic activity has been observed with all-trans-retinoic acid in acute promyelocytic **leukemia**. The mechanisms underlying the anticarcinogenic and antitumor activities of retinoids appear to be associated with their ability to modulate the growth and differentiation of normal, premalignant and malignant cells in vitro and in vivo. Most of these effects are mediated by nuclear retinoid receptors; however, other mechanisms may also be involved. This review summarizes the studies which indicate that retinoids are potentially useful agents for cancer chemoprevention and therapy.

L5 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:329588 CAPLUS
DN 129:89885
TI Potent retinoid synergists with a diphenylamine skeleton
AU Ohta, Kiminori; Tsuji, Motonori; Kawachi, Emiko; Fukasawa, Hiroshi; Hashimoto, Yuichi; Shudo, Koichi; Kagechika, Hiroyuki
CS Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, 113-0033, Japan
SO Biological & Pharmaceutical Bulletin (**1998**), 21(5), 544-546
CODEN: BPBLEO; ISSN: 0918-6158
PB Pharmaceutical Society of Japan
DT Journal
LA English
AB 4-[N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)amino]benzoic acid (I) exhibited weak retinoidal and retinoid synergistic activities in HL-60 cell differentiation assay. N-Alkylation of I caused decrease or loss of differentiation-inducing activity, but enhanced the synergistic activity with a synthetic retinoid Am80, as reflected in the potent synergistic EC50 (SEC50) values of DA023 (1.6+10-10 M) and DA113 (1.4+10-10 M) in the presence of 1.0+10-10 M Am80. The structure-activity relationships indicate that diphenylamine compds. elicit their activities through nuclear receptors, probably retinoic acid receptors (RARs) and retinoid X receptors (RXRs) for retinoidal and retinoid synergistic activity, resp.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
AN 1998028860 EMBASE
TI Regulation of retinoidal actions by diazepinylbenzoic acids. Retinoid synergists which activate the RXR-RAR heterodimers.
AU Umemiya H.; Fukasawa H.; Ebisawa M.; Eyrolles L.; Kawachi E.; Eisenmann G.; Gronemeyer H.; Hashimoto Y.; Shudo K.; Kagechika H.
CS H. Kagechika, Graduate Sch. of Pharmaceutical Sci., University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
SO Journal of Medicinal Chemistry, (1997) 40/26 (4222-4234).
Refs: 34
ISSN: 0022-2623 CODEN: JMCMAR
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English

AB In human HL-60 promyelocytic **leukemia** cells, diazepinylbenzoic acid derivatives can exhibit either antagonistic or synergistic effects on the differentiation-inducing activities of natural or synthetic retinoids, the activity depending largely on the nature of the substituents on the diazepine ring. Thus, a benzolog of the retinoid antagonist LE135 (6), 4-(13H- 10,11,12,13-tetrahydro-10,10,13,13,15-pentamethyldinaphtho[2,3-b][1,2- e]diazepin-7-yl)benzoic acid (LE540, 17), exhibits a 1 order of magnitude higher antagonistic potential than the parental LE135 (6). In contrast, 4- [5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl]- benzoic acid (HX600, 7), a structural isomer of the antagonistic LE135 (6), enhanced HL-60 cell differentiation induced by RAR agonists, such as Am80 (2). This synergistic effect was further increased for a thiazepine, HX630 (29), and an azepine derivative, HX640 (30); both synergized with Am80 (2) more potently than HX600 (7). Notably, the negative and positive effects of the azepine derivatives on retinoidal actions can be related to their RAR-antagonistic and RXR-agonistic properties, respectively, in the context of the RAR-RXR heterodimer.

L5 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:77935 CAPLUS
DN 128:200668
TI Alterations of differentiation, clonal proliferation, cell cycle progression and bcl-2 expression in RARα-altered sublines of HL-60
AU Grillier, I.; Umiel, T.; Elstner, E.; Collins, S. J.; Koeffler, H. P.
CS Division of Hematology/Oncology, Cedars-Sinai Medical Center/UCLA School of Medicine, Los Angeles, CA, 90048, USA
SO Leukemia (**1997**), 11(3), 393-400
CODEN: LEUKED; ISSN: 0887-6924
PB Stockton Press
DT Journal
LA English
AB All-trans retinoic acid (RA) induces granulocytic differentiation of acute promyelocytic **leukemia** cells both in vivo and in vitro. In the HL-60 wild-type (WT) early promyelocytic **leukemia** cell line, granulocytic differentiation appears to be directly mediated by the nuclear receptor RARα. An HL-60 subline resistant to RA (HL-60 R) contains a point mutation which results in a truncation of 52 amino acids at the COOH end of RARα. Cross-talk between differentiation, clonal inhibition of growth and apoptosis was studied using HL-60 WT, HL-60 R, and HL-60 R infected by a retroviral vector containing RARα (LX) as targets, which were cultured with various retinoids, vitamin D3 analogs, HMBA, or DMSO. None of these compds. induced significant differentiation of HL-60 R and HL-60 LX, but they did induce differentiation of HL-60 WT. In contrast, retinoids inhibited the clonal proliferation of HL-60 WT, HL-60 R, and HL-60 LX. Vitamin D3 analogs including KH 1060 stimulated the clonal growth of HL-60 R; but they inhibited clonal growth of HL-60 WT and LX. Levels of Bcl-2 strongly decreased in HL-60 WT and LX after treatment by retinoids, while no change in expression occurred in HL-60 R. Neither KH 1060 nor 9-cis RA induced apoptosis of HL-60 R, but these agents did induce apoptosis in HL-60 LX WT. Taken together, the authors showed that HL-60 R has a global defect in its ability to be induced to differentiate by a variety of pathways, not merely the retinoid pathway. Furthermore, the authors' HL-60 models showed that inhibition of proliferation and induction of apoptosis and differentiation can be dissociated Clin., these results suggest that several putative differentiation agents may have anti-cancer (antiproliferative) activities, even though they do not induce differentiation of the cancer cells.
RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:800326 CAPLUS

DN 128:110536
TI Potentiation of VD-induced monocytic **leukemia** cell differentiation by retinoids involves both RAR and RXR signaling pathways
AU Defacque, H.; Sevilla, C.; Piquemal, D.; Rochette-Egly, C.; Marti, J.; Commes, T.
CS Laboratoire de Biologie Cellulaire, INSERM U431, Universite de Montpellier II, Montpellier, 34095, Fr.
SO Leukemia (**1997**), 11(2), 221-227
CODEN: LEUKED; ISSN: 0887-6924
PB Stockton Press
DT Journal
LA English
AB Retinoids and vitamin D (VD) cooperate to induce the differentiation and inhibit the proliferation of human myelomonocytic **leukemia** cells. Two classes of retinoids receptors, the RARs and RXRs, resp., can mediate these effects. RXR forms heterodimers with a variety of nuclear receptors, including RAR and the VD receptor. We have previously found that VD treatment increases RXRα levels in myelomonocytic **leukemia** cells. By immunoanal., we observed in the present work that the RARα protein is expressed in proliferating U937, HL-60 and THP-1 human **leukemia** cells and that VD treatment induces alterations of its electrophoretic pattern, although with large differences between cell lines. In the three cell lines, 9-cis RA, an agonist of both RARs and RXRs, cooperated with VD more efficiently than all-trans RA and RAR-specific synthetic ligands, thus suggesting an involvement of both RAR and RXR pathways in cell differentiation. Using U937 cells as a model, we delineated the relative contributions of RAR and RXR by assessing the effects of receptor-selective synthetic retinoids. The synergy between VD and all-trans RA or RAR-specific agonists (TTNPB and Ro 40-6055) was abrogated by a RARα-specific antagonist (Ro 41-5253), confirming an involvement of RARα. However, the cooperation between VD and 9-cis RA, although reduced, was not suppressed by the antagonist, suggesting also an involvement of the RXR pathway. The role of RXR as a ligand-activated receptor was confirmed using RXR-specific agonists (CD2608 and LGD1069), which also proved able to cooperate with VD. Finally, while each synthetic agonist alone was significantly less potent than 9-cis RA, combinations of the RAR and RXR selective agonists TTNPB and LGD1069 appeared to be as effective as the pan agonist 9-cis-RA. These results confirm that various retinoids can cooperate with VD and demonstrate that, at a whole cell level, optimal effects require the activation of both RAR and RXR receptors.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 16 EMBASE
on STN DUPLICATE 2
AN 96069580 EMBASE
DN 1996069580
TI Effects of novel retinoid X receptor-selective ligands on myeloid leukemic differentiation and proliferation in vitro.
AU Kizaki M.; Dawson M.I.; Heyman R.; Elstner E.; Morosetti R.; Pakkala S.; Chen D.-L.; Ueno H.; Chao W.-R.; Morikawa M.; Ikeda Y.; Heber D.; Pfahl M.; Koeffler H.P.
CS Division of Hematology/Oncology, 8700 Beverly Blvd,Los Angeles, CA 90048, United States
SO Blood, (1996) 87/5 (1977-1984).
ISSN: 0006-4971 CODEN: BLOOAW
CY United States
DT Journal; Article
FS 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English

SL English
AB The biologic effects of retinoids such as all-trans-retinoic acid (ATRA) and 9-cis-retinoic acid on proliferation and differentiation of hematopoietic cells are mediated by binding and activating two distinct families of transcription factors: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). The RARs require heterodimerization with RXRs; in addition, RXRs can form homodimers, which can bind to DNA response elements that are either distinct or the same as those bound by the RAR/RXR heterodimers. Therefore, the two retinoid pathways provide sequences that are specific for effective DNA binding and activation of target genes. We have developed several series of novel synthetic retinoids that selectively interact with RXR/RXR homodimers and RAR/RXR heterodimers. We show here that SR11236 and SR11246, which are RXR-selective analogs, had little ability to inhibit clonal growth and induce differentiation of leukemic cells (HL-60 cells and fresh acute myeloid **leukemia** cells). However, SR11249, SR11256, and LGD1069, which activated both RXR/RXR homodimers and RAR/RXR heterodimers, could inhibit clonal growth and induce differentiation of HL-60 cells as well as leukemic cells from patients, including those with acute promyelocytic **leukemia** (APL). This is similar to results observed with RAR/RXR-specific ligands. Interestingly, the combination of ATRA and either SR11249, SR11256, or LGD1069 showed synergistic effects in inducing differentiation of HL-60 cells. A retinoid (SR11238) with strong anti-AP-1 activity that did not activate the RARs and RXRs for gene transcription from the response element TREpal was inactive in our assay systems, suggesting that the antiproliferative effects of retinoids on leukemic cells is not mediated by inhibiting the AP-1 pathway. We conclude that the RAR/RXR pathway is more important than RXR/RXR pathway for differentiation and proliferation of acute myeloid leukemic cells, and certain retinoids or combination of retinoids with both RAR and RXR specificities may synergistically enhance the differentiation activity of ATRA, which may be relevant in several clinical situations.

L5 ANSWER 16 OF 16 EMBASE
on STN DUPLICATE 3
AN 95250967 EMBASE
DN 1995250967
TI Design and synthesis of potent retinoid X receptor selective ligands that induce apoptosis in **leukemia** cells.
AU Boehm M.F.; Zhang L.; Zhi L.; McClurg M.R.; Berger E.; Wagoner M.; Mais D.E.; Suto C.M.; Davies P.J.A.; Heyman R.A.; Nadzan A.M.
CS Dept. of Retinoid Chemistry Research, Ligand Pharmaceuticals, Inc., 9393 Towne Centre Drive,San Diego, CA 92121, United States
SO Journal of Medicinal Chemistry, (1995) 38/16 (3146-3155).
ISSN: 0022-2623 CODEN: JMCMAR
CY United States
DT Journal; Article
FS 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Structural modifications of the retinoid X receptor (RXR) selective compound 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid (LGD1069), which is currently in phase I/IIA clinical trials for cancer and dermatological indications, have resulted in the identification of increasingly potent retinoids with > 1000-fold selectivity for the RXRs. This paper describes the design and preparation of a series of RXR selective retinoids as well as the biological data obtained from cotransfection and competitive binding assays which were used to evaluate their potency and selectivity. The most potent and selective of the analogs is 6-[1(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2- yl)cyclopropyl]nicotinic acid (12d; LG100268).

This compound has proven useful for investigating RXR dependent biological pathways including the induction of programmed cell death (PCD) and transglutaminase (TGase) activity. Our studies indicate that the induction of PCD and TGase in human leukemic myeloid cells is dependent upon activation of RXR-mediated pathways.

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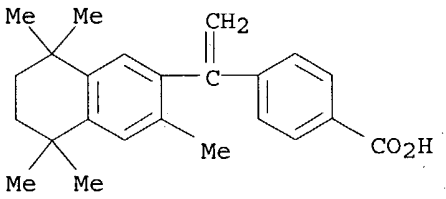
L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 153559-49-0 REGISTRY
CN Benzoic acid, 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Bexarotene**
CN LG 100069
CN LG 1069
CN LG 69
CN LG 69 (retinoid)
CN LGD 1069
CN RO 26-4455
CN SR 11247
CN Targret
CN **Targretin**
CN Targretyn
CN Targrexin
FS 3D CONCORD
MF C24 H28 O2
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN, DIOGENES, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L14 ANSWER 26 OF 84 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:142526 CAPLUS
DN 126:207105
TI Initial clinical trial of a selective retinoid X receptor ligand, LGD1069
AU Miller, Vincent A.; Benedetti, Fabio M.; Rigas, James R.; Verret, Amy L.; Pfister, David G.; Straus, David; Kris, Mark G.; Crisp, Mira; Heyman, Richard; et al.
CS Thoracic Oncology, Genitourinary Oncology, Developmental Chemotherapy, Leukemia, and Lymphoma Services, Divisions of Solid Tumor and Hematologic Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, NY, 10021, USA
SO Journal of Clinical Oncology (**1997**), 15(2), 790-795
CODEN: JCONDN; ISSN: 0732-183X
PB Saunders
DT Journal
LA English
AB The retinoid response is mediated by nuclear receptors, including retinoic acid receptors (RARs) and retinoid "X" receptors (RXRs). All-trans retinoic acid (RA) binds only RARs, while 9-cis RA is an agonist for both RARs and RXRs. Recently, LGD1069 was identified as a highly selective RXR agonist with low affinity for RARs. The authors undertook a dose-ranging study to examine the safety, clin. tolerance, and pharmacokinetics of LGD 1069 in patients with advanced **cancer**. Fifty-two patients received LGD 1069 administered orally once daily at doses that ranged from 5 to 500 mg/M2 for 1 to 41 wk. Treatment proceeded from a starting dose of 5 mg/M2. Pharmacokinetic sampling was performed on selected patients on days 1, 15, and 29. Reversible, asymptomatic increases in liver biochem. tests were the most common dose-limiting adverse effect. Less prominent reactions included leukopenia, hypertriglyceridemia, and hypercalcemia. Characteristic retinoid toxicities, such as cheilitis, headache, and myalgias/arthralgias, were mild or absent. Two patients with cutaneous T-cell lymphoma experienced major antitumor responses. Pharmacokinetic studies obtained in 27 patients at eight dose levels showed that the day 1 area under the plasma concentration-times-time curves (AUCs) were proportional to dose. At all dose studied, the day 1 AUCs were similar to those on days 15 and 29, indicating a lack of induced metabolism LGD 1069 is a unique compound that exploits a newly identified pathway of retinoid receptor biol. that may be relevant to tumor-cell proliferation and apoptosis. Further investigation of this drug is warranted. Based on the results of this study, a dose of 300 mg/M2 is recommended for single-agent trials.